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10/593,683	09/20/2006	Mingjun Huang	API0005US2	9081

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,683	HUANG ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20,21,23,31,33,36,51 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18,20,21,23,51 and 52* is/are allowed.

6)☒ Claim(s) *31,33 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's response filed 03/29/2010 is acknowledged. Claims 18, 20, 21, 23, 31, 33, 36, 51 and 52 are pending in the application. The objections regarding the oath/declaration and specification made in the Office action mailed 01/13/2010 are withdrawn in view of Applicant's corrective amendment and ADS.

The rejection of claim 23 under 35 USC 112, 2nd paragraph is withdrawn in view of Applicant's amendment.

The rejection of claims 31 and 36 under 35 USC 103(a) is maintained for the reasons of record and reiterated below. Applicant's arguments will be addressed following the rejection.

Claim 33 has been added to the rejection. Previously, the examiner had construed "isolating…from the cell membrane fraction of the transfected cells" as meaning that the replicase complex was *separated* from the membrane fraction. However, based on the specification, it appears the claim is more properly construed to mean that the isolated complex is isolated by separating the membrane fraction from the rest of the cellular material; i.e. the isolated complex is the membrane fraction. See specification at page 6, paragraph [0016]:

" 'Isolated replicase complex' includes the membrane fraction of a cell expressing the viral replicase RNA. The isolated replicase complex may be separated from the cell nucleus, chromosomal DNA, and cytoplasmic materials, for example."

See also specification, page 6, paragraph [0018] and page 15, paragraph [0048].

Since this constitutes a new rejection of claim 33 that is not necessitated by amendment, this action will be made NON-FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 33 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Zhong et al (Antimicrobial Agents and Chemotherapy 47(8):2674-2681, August 2003, cited on the IDS of 09/20/2006) and Mueller et al (Journal of Biological Chemistry 261(25):11756-11764, September 1986).

With regard to claims 31 and 36, Hardy teaches a method for determining whether a test compound is an RNA synthesis inhibitor of a positive strand RNA virus (specifically hepatitis C virus) comprising:

contacting an isolated replicase complex for the positive strand RNA virus (Abstract: "A number of hepatitis C virus (HCV) proteins, including NS5B, the RNA-dependent RNA polymerase, were detected in membrane fractions from Huh7 cells containing autonomously replicating HCV RNA replicons. These membrane fractions were used in a cell-free system for the analysis of HCV RNA replication." Page 2031, column 2, last paragraph: "The P15 fractions enriched for HCV nonstructural proteins were assayed for replicase activity in the presence of a reaction mix...". Page 2030, paragraph bridging columns 1-2: "…we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase."),

an isolated viral replicon template RNA for the positive strand RNA virus (Page 2031, column 1, first paragraph of "Results": "The replicon RNA…was derived from the HCV genotype 1b…". Page 2031, column 2, last paragraph: "Since no additional RNA is added to the in vitro reaction mixture, the template corresponds to the endogenous replicon RNA."),

nucleotides (Page 2031, column 2, last paragraph: "…cold nucleoside triphosphates (NTPs)…". See also last paragraph, page 2030.),

and a labeled nucleotide analog (Page 2031, column 2, last paragraph: "…including [^{32}P]CTP…". See also last paragraph, page 2030.),

and the test compound (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…".)

under conditions sufficient for in vitro RNA synthesis, to form a newly synthesized RNA population comprising the labeled nucleotide analog (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…After this preincubation period, the remaining components of the standard replication reaction were added...and the reactions continued for 1 h at 34°C.");

detecting the newly synthesized RNA population comprising the labeled nucleotide analog (See figure 7. See also Materials and Methods, paragraph entitled "In vitro HCV RNA synthesis" bridging pages 2030-2031.);

quantitating the newly synthesized RNA population comprising the labeled nucleotide analog to provide a test RNA amount (See figure 7 caption: "...quantitated by using a phosphorimager...".);

and comparing the test RNA amount with a control RNA amount of a control newly synthesized RNA population comprising the labeled nucleotide analog produced in the absence of the test compound (See figure 7; the graph clearly indicates a 0 μM inhibitor data point, which represents a reaction performed in the absence of the inhibitor, i.e. test compound.)

wherein a decrease in the test RNA amount compared to the control RNA amount indicates that the test compound inhibits RNA synthesis of the positive strand RNA virus (See figure 7, which indicates that the amount of test RNA, as measured by the incorporation of the labeled nucleotide, decreases with increasing concentration of inhibitor.).

With regard to claim 33, Hardy used membrane fractions (see figure 1 and "Materials and Methods", section headed by "Cellular fractionation").

Hardy does not teach *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog, under stringent conditions, wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population; digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog; detecting the protected RNA population comprising the labeled nucleotide analog; quantitating the protected RNA population comprising the labeled nucleotide analog; and comparing the test RNA amount with a control RNA amount of protected RNA* to determine whether *the test compound inhibits RNA synthesis initiation of the positive strand virus*.

In other words, the difference between the claimed invention and Hardy is that Hardy does not carry out and RNase protection assay using a probe to the RNA synthesis (transcription) initiation region to assess RNA synthesis *initiation* (Hardy just quantifies the final transcript).

Zhong taught dinucleotide analogs as inhibitors of hepatitis C virus, specifically as inhibitors of RNA synthesis initiation:

Abstract: "Because the initiation process is a rate-limiting step in viral RNA replication, inhibitors that interfere with the initiation process will have advantages in suppressing virus replication."

Page 2674, last paragraph: "The use of dinucleotide analogues as inhibitor molecules to target the initiation step of viral RNA synthesis represents a novel approach to antiviral interference."

It was known in the prior art to hybridize a probe to the transcription initiation region of a transcript followed by RNase digestion to assess transcription initiation. As in the claimed methods, Mueller synthesized newly transcribed RNA comprising a labeled nucleotide analog and hybridized the newly synthesized RNA with a probe (unlabeled), followed by digestion of the unprotected RNA.

In particular, Mueller taught an assay comprising *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog* (See page 11758, column 1, 2nd and 3rd paragraphs for the synthesis of newly synthesized RNA population comprising a labeled nucleotide analog (i.e. ^{32}P-labeled); see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9; see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an

assessment of the fidelity of transcriptional initiation as well as of the rates of transcription."),

under stringent conditions (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; the term "stringent conditions" does not distinguish over the conditions taught by Mueller),

wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population (see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription.");

digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9);

detecting the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Gel Electrophoresis of the Samples");

quantitating the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Quantitation of the Autoradiogram").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hardy to specifically assess

transcription initiation because Zhong clearly stated that inhibitors of transcription initiation provided advantages. Therefore, one would have been motivated to use the known technique described by Mueller for assessing transcription initiation.

Response to Arguments

Applicant's arguments filed 03/29/2010 have been fully considered but they are not persuasive. Applicant argues (page 8 of the response):

> Applicants respectfully traverse this rejection. Hardy teaches an *in vitro* replication system that can be used to identify inhibitors of RNA synthesis. Such inhibitors may be inhibitors of initiation, but may alternatively be inhibitors of elongation. There is no way to distinguish between the two using the assay of Hardy. In fact, the assay of Hardy was unable to detect *de novo* initiation at all (Hardy page 2033, left column). Accordingly, a person of ordinary skill in the art, wishing to identify inhibitors of initiation, would not choose to start with the assay of Hardy, which is known to be unable to detect such inhibitors. Hardy further does not teach or suggest targeting the initiation region to search for initiation inhibitors, and does not teach or suggest hybridizing a probe complementary to the initiation region of the newly synthesized RNA. Thus, Hardy does not provide an assay capable of detecting inhibitors of RNA synthesis initiation, or any motivation to target the initiation region of newly synthesized RNAs to test for viral RNA initiation inhibitors.

All of the above is true. This is why the rejection is not under section 102, but rather under section 103, in view of the further disclosures of Zhong and Mueller. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues (page 8 of the response):

Zhong is relied upon for the teaching of dinucleotide analogs as inhibitors of RNA synthesis initiation in hepatitis C virus. Zhong's assay uses short RNA templates having the sequence 5' AAAAAAAAGC 3'. Complementary RNA synthesis by the RNA polymerase NS5B is then assayed using GTP and radiolabeled CTP, followed by detection of the radiolabeled pppGpC product (Zhong, Figure 2 and legend). Zhong then uses this assay to detect the effect of dinucleotide analogs on synthesis the product.

Actually, the examiner disagrees with this one. Zhong was relied upon to provide a motivation to identify inhibitors of viral transcription initiation. The rejection does not rely on Zhong's methods or the particular compounds he disclosed, but rather for pointing out the importance of inhibitors of viral transcription initiation:

Abstract: "Because the initiation process is a rate-limiting step in viral RNA replication, inhibitors that interfere with the initiation process will have advantages in suppressing virus replication."

Page 2674, last paragraph: "The use of dinucleotide analogues as inhibitor molecules to target the initiation step of viral RNA synthesis represents a novel approach to antiviral interference."

Applicant continues:

The Examiner views Zhong as supplying the motivation to use the assay of Hardy to identify inhibitors of RNA synthesis initiation, but Applicants respectfully disagree. First, the method used by Zhong differs substantially from the present invention; for example, detection is performed directly by electrophoresis of the labeled product, rather than using an RNase protection assay. Accordingly, Zhong does not teach or suggest hybridizing a probe

complementary to the initiation region of the newly synthesized RNA, as recited in claim 31. In addition, the polymerase used is recombinant, instead of being present within an isolated replication complex. It is unclear whether the inhibitors identified by Zhong would also inhibit initiation by the replication complex. Second, even if there is overlap in the activity of the inhibitors, Zhong fails to teach or suggest the possibility that the assay of Hardy could be modified to detect inhibitors of initiation. As noted above, the Hardy assay was described as being incapable of detecting such inhibitors. Nothing in Zhong addresses this point, or suggests that the Hardy assay might be a useful starting point for developing an assay for initiation inhibitors.

This argument is not persuasive. Again, the rejection does not rely on, nor suggest the use of, Zhong's methods or compounds. Zhong is merely relied upon to provide the motivation to find inhibitors of viral transcription initiation, as opposed to inhibitors of transcription in general.

Applicant argues (page 9 of the response):

Mueller is relied upon for the teaching of RNAse protection assays. Mueller describes such an assay to detect relative rates of transcription of yeast mitochondrial genes *in vivo*, in intact yeast cells. That assay differs from the presently claimed assay in that the present organism is completely different and the present assay is performed in a cell-free system.

Actually the examiner would point out that Mueller taught both *in vivo* transcription in intact yeast cells (page 11758, column 1, section headed by "Labeling and Isolation of Yeast RNA") as well as *in vitro* transcription (page 11758, column 1, section headed by "Labeling RNA by in Vitro Transcription").

Applicant continues:

> It is a substantial leap to apply an assay that is known for use *in vivo* in yeast to a cell-free context, using viral RNA. A person of ordinary skill in the art of molecular biology would be aware that difficulties are commonly encountered when modifying an *in vivo* procedure so as to apply it in an *in vitro* setting, and when switching organisms. Accordingly, Applicants submit that Mueller does not provide a teaching to suggest hybridizing a probe complementary to the initiation region of the newly synthesized RNA in the assay presently claimed.

The examiner disagrees that it would be a substantial leap. Hardy transcribed radiolabeled RNA in vitro (for example, figure 1 and page 2031, section headed by "In vitro replication of HCV replicon RNA"). Mueller also transcribed radiolabeled RNA (either in vivo or in vitro). The only "leap" would have been to perform an RNase protection assay like Mueller's (which, by the way, was an in vitro procedure following the purification of the radiolabeled RNA, regardless of whether the radiolabeled RNA was produced in vivo or in vitro). It is asserted one of ordinary skill in the art could have made this modification, and had a reasonable expectation of success, because both Hardy and Mueller arrive at a point in their techniques where the radiolabeled RNA was purified (e.g. Hardy, figure 3 caption; Mueller, page 11758, paragraphs 2-4). Mueller just adds the extra step of (in vitro) RNase protection assay, a technique well-known in the art.

Applicant concludes:

Mueller further does not teach or suggest that, contrary to the teaching of Hardy, the assay described in Hardy could be modified to identify initiation inhibitors. Even if one were to decide to attempt the assay of Mueller in a cell-free system derived from a different organism, there is simply no basis for concluding that the use of an RNase protection assay with Hardy's system would be an effective way to identify inhibitors of RNA synthesis initiation. This result was not known until the present invention; the cited references, without the application of hindsight, do not teach or suggest this result or provide the motivation to attempt an assay as presently claimed.

If the examiner understands the Applicant, what is being argued is that, because Mueller does not expressly suggest that one should modify *Hardy's* method to arrive at the claimed invention, the rejection is improper. The examiner would like to recite a paragraph from *In re Oetiker,* 977, F.2d 1443, 1448 (CAFC 1992).

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and **if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art**. This **restrictive understanding of the concept of obviousness is clearly wrong**.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, **it is not necessary that the cited references or prior art specifically suggest making the combination**.... In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference." (emphasis provided)

As expressed by the court in *Oetiker*, and reaffirmed in the recent Supreme Court decision, KSR v. Teleflex (82 USPQ2d 1385 (U.S. 2007)), Applicants' contention that the motivation to combine the teaching of prior art must be found in the prior art themselves is simply wrong.

Applicant's statement that there would have been "no basis for concluding that the use of an RNase protection assay with Hardy's system would be an effective way to identify inhibitors of RNA synthesis initiation" (emphasis in original). This argument is not persuasive in view of Mueller's express disclosure of an RNase protection assay for this purpose, stating (page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription." Furthermore, one of ordinary skill in the art would have understood that, if transcription did not initiate, there would be no transcription product to hybridize to the probes overlapping the promoter, and hence no protected fragment would be obtained.

For the reasons discussed above, the rejection is still considered proper and is maintained.

Conclusion

Claims 18, 20, 21, 23, 51 and 52 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637